

**Remarks/Arguments**

Applicants' representative appreciates the courtesies extended during the personal interview of August 20, 2004.

Reconsideration and allowance are respectfully requested in light of this amendment and the following remarks. Applicants have amended the claims to expedite prosecution of the application. This amendment is not intended to acquiesce to the rejections raised by the Examiner and Applicants reserve the right to pursue broader claim subject matter in follow-on applications.

Claims 2-3, 6-9 and 12-34 were withdrawn from consideration. Applicants note that Claims 16-18 are within the scope of elected Group V and should not have been withdrawn.

Claims 35, 36-37 and 40-42 were rejected under 35 USC 112, first paragraph as being overbroad because claims to broadly treating diseases are not allowed. Claims 1, 4-5, 10-11 and 35-43 were rejected under 35 USC 112, second paragraph as being indefinite. Claims 1, 4-5, 10-11 and 35 were rejected under 35 USC 102, as being anticipated by ES462495 (Chem Abstr. 90:87492).

Claims 35, 36-37 and 40-42 were rejected under 35 USC 112, first paragraph as being overbroad because claims to broadly treating diseases are not allowed.

The Examiner has considered the factors of *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). The court in *Wands* relied on the factors set forth in *In re Forman*, 230 USPQ 546, 547 (Bd.Pat.App. & Int. 1986) which address what constitutes "undue experimentation." *Id.* at 737. *Forman* recites factors to be considered in determining whether the practice of a claimed invention would require undue experimentation. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737.

However, it appears that the Examiner has failed to apply the facts of this case to the law articulated in *Wands*. More specifically, the Examiner has failed to consider the synthesis

examples and journal articles relating to inhibition of angiogenesis and treatment of cancers, including breast cancer, renal/kidney cancer, colon cancer, and the like. Applicants contend that both the synthetic examples and the journal articles establishing the target of angiogenesis inhibition in the specification provide sufficient evidence to establish enablement for the reasons that follow.

**1. Quantity of experimentation necessary**

The first factor is the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Here, the disclosure provides guidance on how to make the compounds on pages 95-129, 134-279 and 300-301 (examples 1-475). As in *Wands*, a high level of skill existed at the time of filing with the methods needed to practice the invention. Knowledge of synthetic organic chemistry was well known at the time of filing. Applicants have provided evidence that the level of skill in preparing small molecules according to the present claims was highly developed as of the filing date of the application along with their angiogenesis inhibitory activity. Thus, applicants have provided sufficient evidence to enable one of ordinary skill in the art to practice, without undue experimentation, the claimed invention.

**2. Amount of direction and guidance in the specification**

This factor involves amount of direction provided by the inventor. Here, the inventor has provided disclosure of how to prepare the compounds and use them as inhibitors of angiogenesis activity (see page 95-129, 134-279 and 300-307). Moreover, there are examples of compounds of the present claims prepared according to the disclosure of the present application (Examples 1-475). Thus, the inventors not only teach how to make the compounds, but also teach how to test the compounds for inhibition of angiogenesis and VEGF-related cell proliferation. The skilled artisan would therefore know which compounds would be useful for treating the recited disorders based on the teachings in the specification.

**3. Presence or absence of working examples**

The presence of working examples is the third prong and the present specification provides examples of how to make and use the presently claimed invention. The Examiner contends that there are only speculation and hypothesis in the present specification. Contrary to this conclusion, the specification details how to make the present compounds (pages 95-129, 134-279 and 300-301) and how those compounds inhibit angiogenesis and VEGF-related cell proliferation (pages 302-307). Inhibition of VEGF-related cell proliferation correlates with the recited disorders of the present claims. Unless neovascularization occurs, tumor growth is limited by the diffusion limit for oxygen and does not progress beyond 1 to 2 mm in size. (P. Carmeliet, *Nature Med.*, 6:389-395 (2000)). In experimental models of cancer, blocking angiogenesis prevents tumor growth and/or progression. (F. Scappaticci, *J Clin Onc.*, 20:3906-3927 (2002)) The importance of angiogenesis in human cancer is supported by numerous clinicopathologic correlations, which link the production of proangiogenic substances by the cancer cells or the density of microvasculature in tumors to patient prognosis. (See R. Leek, *Anticancer Res.*, 21:4325-4332 (2001). R. Mehta, et al., *Clin Cancer Res.*, 7:81-88 (2001) and D. Papamichael, *Anticancer Res.*, 21:4349-4354 (2001)). In addition, The ability of in vitro endothelial proliferation assays such as that described in the subject application, to support treatment of VEGF-related angiogenesis and cancer claims is understood to one skilled in the art. See, for example: D. Wang et al., *Am J Phys. Gast. Live Physiology*, 282:G1088-96 (2002). W. Auerbach and R. Auerbach, *Pharmac. Ther.* 63:265-311 (1994). R. Bagley, et al., *Cancer Res.*, 63:5866-73 (2003). L. Hennequin et al., *J. Med. Chem.*, 42:5369-89 (1999). D. Wang et al., *J. Biol. Chem.*, 275:15905-15911 (2000). M. Stewart et al., *Histopath.*, 43:33-39 (2003). Copies of these references are provided in as a courtesy to the Examiner. In addition, the tumor model cited in the specification uses a A431 cell line, which is from a human epithelial squamous carcinoma. The FDA has approved the antioangiogenic bevacizumab for the treatment of colorectal cancer. [See the FDA Press Release dated February 26 2004,

<http://www.fda.gov/bbs/topics/NEWS/2004/NEW01027.html>] Bevacizumab is in clinical trials for a wide number of tumor types including colorectal cancer, breast cancer, non-small cell lung cancer, renal cell carcinoma, melanoma, pancreas tumors, prostate tumors, solid tumors and ovarian tumors. [See <http://www.gene.com/gene/pipeline/trials/>]

**4. Nature of the invention**

The nature of the present invention relates to organic chemistry and therapeutic methodologies involving compounds which are inhibitors of angiogenesis. The compounds of the invention can be prepared using classic techniques found in organic chemistry and prepared by the synthetic protocols herein (see general techniques on pages 95-129, 134-279 and 300-301 (Examples 1-475)). The claimed invention relates to the use of the inventive compounds as inhibitors of angiogenesis and VEGF related cell proliferation for treating various cancers.

**5. State of the prior art**

The state of the prior art is such that inhibition of angiogenesis and VEGF related cell proliferation is known to be indicated in the treatment of disorders such as colon cancer, renal or breast cancer. {See Kerbel and Folkman, Nature Reviews/Cancer, 2:727-739 (2002)}.

**6. Relative skill of those in the art**

The relative skill in the art relates to routine practices of the skilled worker. In the present field, the skilled worker would have to be able to synthesize the compounds of the present claims and be able to treat disorders associated with inhibition of angiogenesis and VEGF related cell proliferation, which include but are not limited to colon cancer, renal or breast cancer.

**7. The predictability or unpredictability of the art**

The level of predictability in the art is another factor to consider. Where there is unpredictability in the art, e.g., in determining whether a compound is an antagonist or an agonist, one skilled in the

art would rely on teachings in the specification as well as teachings of scholarly journals.

**8. Breadth of the claims**

The seventh factor is the breadth of the claims. The Examiner asserts that there are a large number of disorders encompassed by the present claim and that treatment and prevention of cancer is included within the scope of the claimed invention. It is respectfully submitted that just because a large number of disorders may be encompassed by the claims, does not necessitate a lack of enablement. Additionally, while Applicants understand that the rejection is premised on lack of enablement, the Guidelines published by Deputy Commissioner for Patent Policy on Utility (35 U.S.C. § 101) are relevant where it states:

Office personnel should explain why any *in vitro* or *in vivo* data supplied by the applicant would not be reasonably predictive of an asserted therapeutic utility from the perspective of a person of ordinary skill in the art.

. . . As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. An applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use (*emphasis added*).

Based on this position by the Deputy Commission for Patent Policy, the synthetic information and assays presented would appear to adequately enable the present claims. Accordingly, Applicants request reconsideration of the rejections in view of the amended Claims.

Claims 1, 10-11 and 35-43 were rejected under 35 USC 112, second paragraph as being indefinite. Specifically, Claim 1 lacked definition of R<sup>5a</sup>. Applicants request reconsideration of the rejections in view

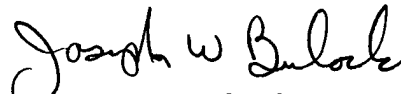
of the amended Claims. Support for the amendment is found in the specification on page 18.

Claims 1, 4-5, 10-11 and 35 were rejected under 35 USC 102, as being anticipated by ES462495 (Chem Abstr. 90:87492). Applicants request reconsideration of the rejections in view of the amended Claims. Applicants assert the presently claimed compounds are novel and unobvious over the art.

A Supplemental IDS is being provided under separate cover.

It is therefore respectfully submitted that Claims 1, 10-11, 16-18, 35-38, 40-41 and 43 are now in condition for allowance. Accordingly, reconsideration and withdrawal of the outstanding rejections, and allowance of Claims 1, 10-11, 16-18, 35-38, 40-41 and 43 are respectfully solicited.

Respectfully submitted,



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